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Medication for Attention Deficit/Hyperactivity Disorder and Risk for Depression: A Nationwide Longitudinal Cohort Study

Zheng Chang[1], **Brian M. D'Onofrio**[2], **Patrick D. Quinn**[2], **Paul Lichtenstein**[1], and **Henrik Larsson**[1,3]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[2]Department of Psychological and Brain Sciences, Indiana University Bloomington, IN, USA

[3]Department of Medical Sciences, Örebro University, Örebro, Sweden

Abstract

Background—Attention-deficit/hyperactivity disorder (ADHD) is associated with high rates of psychiatric comorbidity, including depression. However, it is not yet clear whether ADHD medication increases or decreases the risk for depression.

Methods—We studied all individuals born between 1960 and 1998 and diagnosed with ADHD in Sweden (n=38,752). We obtained data for prescription of ADHD medication, diagnosis of depression and other psychiatric disorders, and socio-demographic factors from population-based registers. The association between ADHD medication and depression was estimated with Cox proportional hazards regression.

Results—ADHD medication was associated with a reduced long-term risk for depression (i.e., three years later), after adjustment for a number of socio-demographic and clinical confounders (HR=0.58, 95% CI: 0.51–0.67). The risk was lower for longer duration of ADHD medication. ADHD medication was also associated with reduced rates of concurrent depression; within-individual analysis suggested that occurrence of depression was 20% less common during periods when patients received ADHD medication compared with periods when they did not (HR=0.80, 95% CI: 0.70–0.92).

Conclusions—Our study suggests that ADHD medication does not increase the risk of later depression; rather, medication was associated with a reduced risk for subsequent and concurrent depression.

Keywords

ADHD medication; depression; stimulants; long-term effect; short-term effect; cohort study

Correspondence to: Zheng Chang, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, 17177, Sweden. zheng.chang@ki.se.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder, affecting up to 10% of children and adolescents (1). ADHD is associated with high rates of comorbidity (2). Depression occurs in youths with ADHD at a significantly higher rate than in youth without ADHD, with rates ranging from 12% to 50% (2, 3). ADHD alone is associated with substantial long-term impairment, morbidity, and mortality (4, 5), and those with ADHD and comorbid depression have even greater risks of adverse outcomes (including suicide) than youths with ADHD or depression alone (6).

Depression in youths with ADHD typically emerges after the onset of ADHD, suggesting the possibility that early diagnosis and treatment of ADHD may have an effect on the risk of developing subsequent depression (7, 8). Stimulant medications (e.g., methylphenidate) are the first-line pharmacological treatments for ADHD and are the most commonly prescribed psychotropic medication in children (9). Although randomized controlled trails (RCTs) have shown that stimulants have beneficial short-term effects on the core symptoms of ADHD, their effect on the development of depression in youth with ADHD is unclear. A series of animal studies has found that early exposure to stimulants may increase the long-term risk of depressive-like behaviors (10–12). Pharmacovigilance studies also identified methylphenidate to be associated with reports of depression (13, 14). In contrast, a few clinical studies following youths with ADHD found null or protective effects of ADHD medication on subsequent depression (7, 15, 16), but these studies have had limited sample sizes, and the results are inconclusive. In addition, the effect of atomoxetine (a non-stimulant medication for treatment of ADHD) on the development of depression in ADHD patients is less studied (17, 18), although the Food and Drug Administration has issued a black box warning regarding the increased risk of suicidal ideation in children and adolescents being treated with atomoxetine (19).

Ascertaining the effect of ADHD medication on the development of depression can provide critical information to clinicians treating youths with ADHD. RCTs are the gold standard for answering such questions, but their ability to explore long-term outcomes is usually constrained by short randomized treatment periods and insufficient follow-up time. For example in the Multimodal Treatment of ADHD (MTA) Study of children, ADHD medication was not associated with any outcome measures at 2 years after randomized treatment ended (20). Population-based studies provide an important alternative to study the long-term effect of medication, with the advantages of large and representative samples and sufficient follow-up time (21).

In this study, we used data from population-based registers in Sweden to explore the association between ADHD medication and depression. Specifically, we assessed two research questions: First, to what extent is ADHD medication associated with the development of later depression? Second, to what extent is ADHD medication concurrently associated with the occurrence of depression? Because previous animal studies and clinical studies have provided contradictory evidence, we did not have a priori hypotheses whether ADHD medication might increase or decrease the risk of depression.

Methods

Study population

We used data from several population-based registers in Sweden, which were linked with unique personal identification numbers (22). The study participants were identified from the National Patient Register, which has nationwide coverage of information on psychiatric in-patient care since 1973 and out-patient visits to specialists (not general practitioners) since 2001. We identified 38,752 patients with a clinical diagnosis of ADHD (ICD-10 code: F90) who were born between 1960 and 1998 and were alive and living in Sweden in 2009. We followed these individuals from January 1, 2006 to December 31, 2009 to explore the association between ADHD medication and depression. The study was approved by the Regional Ethics Committee at Karolinska Institutet, Stockholm, Sweden. All data were anonymized before they were analyzed.

Exposure

We obtained information on ADHD medication from the Prescribed Drug Register, which contains data on all dispensed prescribed drugs in Sweden since July 2005 (23). In this study, we included three stimulants (methylphenidate [N06BA04], amfetamine [N06BA01], and dexamfetamine [N06BA02]) and one non-stimulant (atomoxetine [N06BA09]). For each patient, we divided the follow-up time into treatment periods and non-treatment periods. In Sweden, patients usually refill their prescriptions of ADHD medication within 4 months. Because of poor adherence and periods off treatment during holidays, the time between dispenses might be longer in some cases. In accordance with previous studies (24–26), a treatment period was defined as a sequence of dispensed prescriptions of ADHD medication with no more than 6 months between two consecutive prescriptions. The start of treatment was defined as the date of the first prescription, and the end of treatment was defined as the date of the last prescription. The use of ADHD medication was measured in two ways. First, we ascertained the use of ADHD medication on January 1, 2006 as a binary exposure. Second, we calculated the total duration of ADHD medication between January 1, 2006 and December 31, 2008 (number of years) as a continuous measure, by taking the sum of all treatment periods between 2006 and 2008 for each individual (27).

Outcome

The primary outcome was occurrence of depression between January 1, 2009 and December 31, 2009, includes diagnoses from both hospital admissions and outpatient visits for depression (ICD-10 codes: F32, F33) via the National Patient Register. A secondary outcome was unplanned hospital admissions and outpatient visits for depression between January 1, 2006 and December 31, 2009, which was treated as a time-to-event variable and could occur repeatedly during the follow-up. We included only unplanned visits to avoid misclassifying planned treatments (e.g., regular outpatient visits in treatment programs) as events.

Covariates

The Longitudinal Integration Database for Health Insurance and Labour Market (LISA) collected data on civil, employment, and education status for all individuals aged 16 years or older in Sweden. For individuals aged 16 years or older in 2006, we obtained data on civil, employment, and education status from LISA; and for individuals younger than 16, the values of these variables were set to a separate category ("younger than 16") instead of missing. We identified previous diagnoses of depression and other psychiatric disorders (ICD-10 codes: F00 – F99, except for F32, F33, F90) from the National Patient Register. We also identified if the patients were living in one of the three large cities in Sweden (Stockholm, Göteborg, Malmö) in 2006.

Statistical analyses

To evaluate the long-term effect of ADHD medication on depression, we used Cox proportional hazard models to estimate the associations between ADHD medication in 2006 and depression in 2009 in three steps. We first examined the association in the full sample. Second, we excluded patients with previous diagnoses of depression to further test whether ADHD medication was associated with new onset of depression. Third, we restricted the analyses in patients who were 15 years or younger on January 1, 2006 and without previous diagnoses of depression, because the main concern was in adolescence. In each step, we calculated the hazard ratios (HRs) with adjustment for sex, age and current ADHD medication status (as a time-dependent covariate) in 2009 (Model 1), and in addition, potential confounders at baseline (social-demographic factors and other previous psychiatric disorders; Model 2). To investigate whether time on treatment was important, we carried out separate analyses with the length of ADHD medication as the exposure.

To further clarify the association between ADHD medication and depression, we did three sensitivity analyses in patients without previous diagnoses of depression. First, we performed sensitivity analyses that excluding patients who ever received atomoxetine, because the main concern from animal studies is stimulants. Second, it is possible that some patients were not prescribed medication because they were different (e.g., less severe symptoms, or with comorbid conditions not suitable for medication) from those medicated; therefore, we analyzed a subsample of patients that excluded those who were never treated during follow-up to rule out the potential confounding effect of such unmeasured conditions. Third, to examine the potential influence of misclassification of exposure time, we used a 3-month cutoff (instead of 6-month) to define treatment interval. That is, a treatment period was defined as a sequence of prescriptions without discontinuation within 3 months.

To explore the concomitant effect of ADHD medication on depression, we compared the rate of unplanned visits for depression during periods when patients received medication with periods when the same individuals did not in 2006–2009. We first compared the rates between individuals and then used stratified Cox regression for within-individual comparisons, with each patient as a separate stratum. This method uses the patient as his or her own control, so the analysis adjusts for all confounders that are constant within each individual during follow-up by design (25, 26). Age and use of antidepressant medication were also included as time-varying covariates in the regression models.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Result

Table 1 presents the descriptive statistics for all patients included in this study. We identified 38,752 ADHD patients, of whom 2987 experienced depression events in 2009. Among male patients, 16.8% received ADHD medication on January 1, 2006, and 51.3% received ADHD medication at least once during the period between January 1, 2006 and December 31, 2008, with median length of treatment of 1.2 years (interquartile range [IQR]: 0.5–2.4 years). Corresponding figures in female patients were 10.9%, 48.0%, and 1.0 years (IQR: 0.4–2.0 years), respectively. Supplementary Table S1 shows the baseline characteristics of patients with ADHD with and without ADHD medication. Male patients with ADHD medication were younger than those without medication. Both male and female patients with ADHD medication appeared to have lower rates of depression in 2009 than those without medication. The proportion of female patients experiencing depression in 2009 (11.7%) was twice that of male patients (5.8%).

Long-term effect of ADHD medication (binary measure) on development of depression

In all patients with ADHD, taking medication on January 1, 2006 was associated with a 43% decreased rate of depression in 2009 (HR=0.57, 95% CI: 0.50–0.66, Model 1), and the association remained after adjustment of baseline confounders (HR=0.58, 95% CI: 0.51–0.67, Model 2) (Table 2). We observed similar results in patients without previous depression (HR=0.57, 95% CI: 0.46–0.71) and young patients without previous depression (HR=0.57, 95% CI: 0.40–0.72).

Long-term effect of ADHD medication (continuous measure) on development of depression

For each year an individual was taking ADHD medication during 2006–2008, there was a 21% (HR=0.79, 95%CI: 0.75–0.83) decrease in the rate of depression during 2009, after controlling for baseline confounders (Table 3). Again, we observed similar results in patients without previous depression (HR=0.75, 95% CI: 0.69–0.81) and young patients without previous depression (HR=0.73, 95% CI: 0.63–0.83).

In sensitivity analyses, similar decreases in depression rates associated with ADHD medication were observed when using different exposures or cohorts, that is, when we analyzed stimulant medication (i.e., excluding patients who ever received atomoxetine), excluded individuals who were never treated with ADHD medication, and defined treatment periods using a 3-month cutoff (Table 4).

Concomitant effect of ADHD medication on occurrence of depression

In addition to the long-term effects, we also investigated short-term associations between ADHD medication and occurrence of depression during 2006–2009. Concomitant occurrence of depression was 36% less common during periods when patients received ADHD medication compared with periods when they did not (HR=0.64, 95% CI: 0.58–0.72) (Table 5). Since patients receiving medication might be different from the non-medicated

patients, a within-individual analysis provides a more informative test of the association. The hazard ratio for this within-individual analysis was 0.80 (95% CI: 0.70–0.92), suggesting that ADHD medication decreased the rate of depression by 20% even within individuals (i.e., after adjusting for confounders that do not vary with time, such as genes and childhood environment) and statistically adjusting for antidepressant medication. Similar associations were found when we analyzed stimulant medication only.

Discussion

In this large, population-based cohort study, we followed 38,752 patients with ADHD for 4 years to investigate the association between ADHD medication and depression. The results suggested that ADHD medication was associated with a reduced long-term risk of depression after adjustment for a number of socio-demographic and clinical confounders. The risk was lower for longer duration of ADHD medication. In addition, ADHD medication was associated with reduced rates of concurrent depression, even when using within-individual analyses that adjusted for antidepressant medication.

Results from previous studies on the long-term effect of ADHD medication on the development of depression have been inconsistent. Our finding that ADHD medication reduced the long-term risk of depression is in line with reports from clinical studies of Daviss et al. (7) and Biederman et al. (15). Our results also extended this finding by documenting a similar association for treatment duration and confirming the association while controlling for a number of socio-demographic and clinical confounders. In contrast, the MTA study and the study by Staikova et al. did not find a protective effect of ADHD medication on the development of depression (16, 20). This may be explained by two main methodological differences across studies. First, our sample size was substantially larger than the previous studies, which confers sufficient statistical power to explore the association between ADHD medication and incident depression. Second, our analyses controlled for concurrent medication, which was not taken into account in previous investigation (16).

Consistent with several clinical studies and controlled trials (7, 15, 16, 20), the results of our study indicate no increased risk of depression associated with stimulants, as suggested by animal studies (10–12). One explanation for this discrepancy is that the amount of and manner of managing medication was different in animal studies compared to regular treatment in humans. Another possibility is that the animal model of depressive-like behaviors might not adequately reflect the development of depression in humans. Rather than inducing depression, as suggested in animal studies, efficacious pharmacological treatment may interrupt the pathogenic trajectory from ADHD to depression. ADHD symptoms can lead to problems with academic functioning and social relationships, which may cumulatively contribute to the development of depression in some patients with ADHD (6, 8). ADHD medication can improve academic and social functioning (28), and over time, it may lead to an alternative development trajectory for youths with ADHD, which may decrease the risk of depression and other disorders (15). For example, previous studies have suggested that ADHD medication could protect against later substance use disorder (27, 29).

Similar to a study on suicidal behavior (26), our data suggest a concomitant association between ADHD treatment and lower rates of occurrence of depression. Our findings indicated that ADHD medication might not only protect against the development of depression but also lower the risk of concurrent depression. Although the comorbidity between ADHD and depression is common, the evidence from clinical trials of ADHD medication (e.g., stimulants) are as yet too limited to warrant their use as treatment adjuncts for depression in selected patient groups (30). A recent clinical trial reported that the addition of methylphenidate to citalopram demonstrated an enhanced clinical response profile in mood and well-being, as well as a higher rate of remission, in older patients (31). Whether such effect would extend to other age groups warrants further investigation. We also noticed that among ADHD patients with comorbid depression, the rate of antidepressants use appeared to be lower in patients without ADHD medication (57%) than those with ADHD medication (70%). It is possible that a tendency to avoid treatment for one condition might lead to avoidance for another one.

The strengths of our study include the population-based sample, longitudinal design, time-sensitive measures of ADHD medication, and careful adjustment of potential confounders. To the best of our knowledge, this is the first national-wide longitudinal study investigating the association between ADHD medication and depression. Data from population-based registers provided a representative sample, which included patients who for various reasons would not be included in clinical trials. However, observational studies, especially pharmacoepidemiological studies, are subject to bias from selection effects (32). The biggest threat is that patients who received medication might be different from those without medication (usually more symptoms or with comorbid conditions). Unlike RCTs, observational studies, such as ours, cannot account for all possible confounders that select individuals into treatment. We have adjusted for a number of socio-demographic and clinical factors when exploring the long-term effect of ADHD medication on depression, and we conducted sensitivity analyses excluding those who were never treated during follow-up. In addition, we used a within-individual analysis when studying the concomitant effect of ADHD medication on depression, which adjusts for all potential confounders that are constant during the follow-up (e.g., genetic predisposition and early environment) and adjusted for antidepressant use. Nevertheless, unmeasured and time-varying confounders can never be fully ruled out in our study. Thus, causal inferences based solely on observational studies should be avoided.

The findings should also be considered in the context of other limitations. First, the ascertainment of psychiatric diagnoses relied on data from patient registers. Although these registers have good diagnostic validity on ADHD (33) and depression (34) and the important advantage of not requiring accurate respondent recall and reporting, they most probably capture the more severe cases of depression (e.g., those that lead to outpatient specialist care or hospitalization). Second, because about 90% of the patients receiving atomoxetine had also taken psychostimulants in the past, we were not able to explore the specific effect of non-stimulant medication on depression. However, the magnitude of the associations was similar when considering all medication and stimulant medication only. Third, we did not have information on daily dosage or age of initiation of treatment for all the patients. Future studies are needed to explore whether doses or age of initiation could moderate the

association between ADHD medication and depression. Finally, the findings are based on Swedish population data. Although Sweden does not appear to be unusual in rates of ADHD and ADHD medication (35, 36), generalization to other cultures/countries should be made with caution.

Our study provided new evidence that ADHD medication does not increase the risk of later depression but rather is associated with a reduced risk for subsequent and concurrent depression. This finding supports the recommendation of the European ADHD Guidelines Group that ADHD medications are not contraindicated in case of comorbid depression, although caution is required when prescribing to children and adolescents with suicidal ideation/attempts (37). When making treatment decisions for ADHD, clinicians have to weigh the harms and benefits of the medication. If confirmed by other studies and designs, our findings provide supports *for* rather than *against* pharmacological treatment of ADHD, especially when considering the presence of comorbidity or probable future development of depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of patients with ADHD.

	Men (n=26,249)	Women (n=12,503)
Received ADHD medication on January 1, 2006	4415 (16.8%)	1362 (10.9%)
Received any ADHD medication 2006–2008	13,463 (51.3%)	5996 (48.0%)
Depression in 2009	1529 (5.8%)	1458 (11.7%)
Age in 2006		
8–15	12,961 (49.4%)	4319 (34.5%)
16–25	7805 (29.7%)	4098 (32.8%)
26–35	3018 (11.5%)	2120 (17.0%)
36–46	2465 (9.4%)	1966 (15.7%)
Civil status in 2006		
Unmarried	11,816 (45.0%)	6287 (50.4%)
Married	813 (3.1%)	1020 (8.1%)
Divorced	646 (2.4%)	863 (6.9%)
Widowed	13 (0.1%)	14 (0.1%)
Younger than 16 years old	12,961 (49.4%)	4319 (34.5%)
Employed in 2006		
Yes	3113 (11.8%)	2059 (16.5%)
No	10,175 (33.8%)	6125 (49.0%)
Younger than 16 years old	12,961 (49.4%)	4319 (34.5%)
In school in 2006		
Yes	4326 (16.5%)	2648 (21.2%)
No	8962 (34.1%)	5536 (44.3%)
Younger than 16 years old	12,961 (49.4%)	4319 (34.5%)
Living in a metropolitan area in 2006	3523 (13.4%)	1723 (13.8%)
Other psychiatric disorders before 2006	8951 (34.1%)	4625 (37.0%)

Table 2

Hazard ratios (95% CI) for associations between ADHD medication in 2006 and depression in 2009.

	Number of patients	Number of outcomes	Model 1: adjusted for sex, age, and ADHD medication in 2009	Model 2: as in model 1 + other potential confounders 2006*
Full sample	38,752	2987	0.57 (0.50–0.66)	0.58 (0.51–0.67)
Individuals without previous depression	36,964	1200	0.54 (0.44–0.76)	0.57 (0.46–0.71)
Youth without previous depression	16,966	331	0.55 (0.39–0.78)	0.57 (0.40–0.82)

* In addition to model 1, adjusted for adjusted for socio-demographic measures (civil status, employment, study, living in metropolitan area, family income) and history of other psychiatric disorders (except for ADHD and depression).

Table 3

Hazard ratios (95% CI) for associations between duration of ADHD medication 2006–2008 and depression in 2009.

	Number of patients	Number of outcomes	Model 1: adjusted for sex, age, and ADHD medication in 2009	Model 2: as in model 1 + other potential confounders 2006*
Full sample	38,752	2987	0.77 (0.73–0.81)	0.79 (0.75–0.83)
Individuals without previous depression	36,964	1200	0.72 (0.67–0.78)	0.75 (0.69–0.81)
Youth without previous depression	16,966	331	0.72 (0.63–0.82)	0.73 (0.63–0.83)

Note: the hazard ratio is the ratio of the hazard rates associated with one year increase in the duration of ADHD medication.

*In addition to model 1, adjusted for adjusted for socio-demographic measures (civil status, employment, study, living in metropolitan area, family income) and history of other psychiatric disorders (except for ADHD and depression).

Table 4

Sensitivity analyses for long-term associations between ADHD medication and depression in 2009.

Analysis	Number of patients	Number of outcomes	Adjusted hazard ratio (95% CI)
Stimulant medication in 2006 in patients excluding those ever received atomoxetine [a]	30,756	2278	0.51 (0.43–0.60)
Duration of stimulant medication 2006–2008 in patients excluding those ever received atomoxetine [b]	30,756	2278	0.77 (0.72–0.82)
ADHD medication in 2006 in patients excluding those who never received medication [a]	19,459	1223	0.66 (0.57–0.76)
Duration of ADHD medication 2006–2008 in patients excluding those who never received medication [b]	19,459	1223	0.84 (0.79–0.89)
Duration of stimulant medication 2006–2008 using a 3-month cutoff to define treatment interval [b]	38,752	2987	0.84 (0.77–0.91)

[a]The hazard ratio is the ratio of the hazard rates between those with and without ADHD medication on January 1, 2006.

[b]The hazard ratio is the ratio of the hazard rates associated with one year increase in the duration of ADHD medication.

Table 5

Concomitant effect of ADHD medication on occurrence of depression in 2006–2009.

	Number of patients	Number of outcomes	Between-individual [a]	Within-individual [b]
ADHD medication in full sample	38,752	4820	0.64 (0.58–0.72)	0.80 (0.70–0.92)
Stimulant medication in patients excluding those ever received atomoxetine	30,756	3634	0.58 (0.50–0.66)	0.67 (0.57–0.80)

[a] Hazard ratios were calculated with Cox regression, adjusted for sex, age, and use of antidepressants.

[b] Hazard ratios were calculated with stratified Cox regression, adjusted for all unmeasured covariates that are constant within each individual during the follow-up and measured time-varying covariates (i.e., age, and use of antidepressants).